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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/520,130	03/07/2000	Robert Arathoon	P1099R2	1353

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 06/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/520,130	ARATHOON ET AL.	
	Examiner	Art Unit	
	Anne L. Holleran	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/21/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/16/2006 has been entered.

2. The amendment filed 3/16/2006 is acknowledged. Claims 47-63 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

4. The objection to claims 59 and 60 for the phrase ""variable light chain domain" is withdrawn in view of the amendment.

Claim Rejections Maintained:

Double Patenting

5. The provisional rejection of claims 47-63 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 88-109 of copending

Application No. 09/863,693 is maintained for the reasons of record. Applicants have indicated that upon an indication of allowable subject mater, a terminal disclaimer may be filed, if appropriate.

6. The provisional rejection of claims 47-63 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30-43, 45- 51 and 53-55 of copending Application No. 09/373,403 is maintained for the reasons of record. Applicants have indicated that upon an indication of allowable subject mater, a terminal disclaimer may be filed, if appropriate.

7. The provisional rejection of claims 47-63 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 45-82 of copending Application No. 10/143,437 is maintained for the reasons of record. Applicants have indicated that upon an indication of allowable subject mater, a terminal disclaimer may be filed, if appropriate.

Claim Rejections - 35 USC § 112

8. Claims 47-52 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicants' arguments have been carefully considered but fail to persuade. Applicants point to page 97, line 28 – page 98, line 3 as support for the concept of multispecific antibodies comprising more than one light chain, where the light chains have at least 98% sequence identity and only differ from one another at amino acid positions outside of the CDR regions. The passage pointed to appears to be a discussion concerning whether one may substitute one light chain for another in a specific scFv ("Alternatively, according to the invention, such light chains having 98-99% sequence identity with the light chian of a prospective paired scFv (Axl.78, for example) may be substituted with the paired light chain and retain binding specificity"). This sentence does not appear to be support for the concept of multispecific antibodies having more than one light chain, but instead appears to be support for making alternative versions of specific scFv molecules.

Applicants have also presented arguments that appear to be directed to enablement of the claimed inventions, when applicants assert that given the statement on pages 97-98, which concerns substitution of one light chain for another in an scFv, would enable one of skill in the art to use alternative versions of scFvs to make the claimed bispecific antibodies. However, the basis for this rejection is that the specification fails to provide written support for the claimed inventions because nowhere in the specification is there support for the concept of a bispecific antibody having two different light chains. Applicant is reminded that the description requirement is severable from the enablement requirement. Furthermore, it is noted that entitlement to a filing date does not extend to subject matter, which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

Therefore, the rejection is maintained for the reasons of record.

The original rejection is reiterated below:

The basis for this rejection is that the amendment to the specification to recite claims drawn to methods of making multispecific antibodies comprising binding domains, where the binding domains are made up of a heavy and light chain, and where the light chain is not the same for all of the binding domains is not supported by the specification. Therefore, the recitation of claim 30 "where the light chains of the first and additional polypeptides each have three CDR regions, and have at least 98% sequence identity and only differ from one another at amino acid positions outside of the CDR regions" is not supported by the specification as originally filed. The specification teaches methods of making multispecific antibodies, where the each of the binding domains comprises a "common light chain". The specification defines "common light chain" or "common amino acid sequence of the light chain" on page 21, and as an amino acid sequence of ***the*** light chain in the multispecific antibody. There does not appear to be any contemplation of multispecific antibodies comprising more than one light chain (i.e., there appears to be only the contemplation that the same light chain is used for all of the binding domains present in the multispecific antibody). Even a difference of 1 amino acid between the two light chains results in a bispecific antibody having two different light chains, and there is no support in the specification that demonstrates that applicant conceived of a method of making multispecific antibodies having two different light chains. Other instances in the specification that indicate that applicant conceived of methods of making bispecific antibodies where all of the binding domains comprise a light chain having the same sequence is found at page 13, lines 14-

21; page 22, line 15 – page 23, line 12; page 27, lines 2-5; page 56, lines 10-26; page 95, lines 25-28; and page 104, line 22 – page 105, line 26.

Applicants have pointed to passages (page 97-98) in the specification and assert that these passages provide support for the concept of multispecific antibodies comprising light chains where the light chains have at least 98% sequence identity to each other and only differ from one another at amino acid positions outside the CDR regions. However, this teaching of the specification appears to be directed to the process of selecting a light chain that will be used in the process of making a multispecific antibody (i.e. selecting a common light chain). The teachings on page 97 of the specification do not provide support for bispecific antibodies having two different light chains, but instead are directed to a process for identifying one light chain that may be useful in making a bispecific antibody. Applicant is reminded that the description requirement is severable from the enablement requirement.

New Grounds of Rejection:

9. Claims 47, 52-54 and 58 are rejected under 35 U.S.C. 102(b) as being anticipated by Nissim (Nissim, A. et al., The EMBO Journal, 13(3): 692-698, 1994; cited in IDS) as evidenced by Merchant (Merchant, A.M. et al, Nature Biotechnology, 16: 677-681, 1998; cited in IDS).

Nissim teaches methods for expressing scFv fragments in *E. coli* from a phage library. Merchant teaches that the phage library of Nissim is library that has extensive H chain repertoires and unique L chain sequence, thus each antibody fragment derived from the phage library of Nissim has the same L chain (see page 677, 1st column). Nissim also teaches the making of "polyclonal" supernatants, which appear to be supernatants that contain scFv

fragments with multiple specificities. In addition, Nissim teaches that dimerization occurs in the supernatants, especially when the supernatant has been concentrated (see 695, 2nd column). Nissim teaches that for polyclonal scFv fragments, the supernatant was concentrated. The dimerization appears to occur through the binding of an L chain region from one chain binding to an H chain region from another chain. Therefore, Nissim inherently teaches the claimed bispecific antibodies and compositions comprising said antibodies.

10. Claims 59, 60, and 63 are rejected under 35 U.S.C. 102(b) as being anticipated by Hu (Hu, S. et al., Cancer Res. 56: 3055-3061, 1996).

Claims 59, 60, 62 and 63 read on divalent scFv constructs, because the claims fail to recite that the each of the binding domains binds to different antigens.

Hu teaches that single chain Fv constructs can be made divalent by fusing the single chain antibody chains with C_H3 regions (see page 3056, Figure 1); and also teaches the "flex minibody" in which the C_H3 is fused to a hinge region, which contains cysteine residues for the formation of disulfide bonds, which further stabilize the dimmer (see page 3059, 1st column) Therefore, Hu teaches the claimed antibodies.

11. Claims 47, 48, 50, 52-54, 56, and 58 are rejected under 35 U.S.C. 102(b) as being anticipated by de Kruif (de Kruif et al., The Journal of Biological Chemistry, 271(13): 7630-7634, 1996, March) as evidenced by Merchant (supra).

de Kruif teaches a method for making bispecific scFv antibodies that contain IgG3 hinge regions and either a Fos or Jun leucine zipper to the scFv proteins. To increase stability of the

bispecific antibodies, cysteine residues are incorporated into the leucine zippers, facilitiating disulfide bridge formation. The nucleic acid encoding the dimerization regions (IgG3 together with the leucine zippers and cysteine residues) are dimerization cassettes that are introduced into the NotI restriction sites of genes encoding scFvs isolated from a variety of phage display libraries, such as Nissim (see page 7632, 2nd column). Merchant provides evidence that the library of Nissim is a library that has extensive H chain repertoires and unique L chain sequence. Thus, each antibody fragment derived from the phage library of Nissim has the same L chain (see page 677, 1st column). Therefore, de Kruif provides bispecific antibodies that are the same as that claimed.

12. Claims 47-49, 52-55, 58-61 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over de Kruif (de Kruif et al., The Journal of Biological Chemistry, 271(13): 7630-7634, 1996, March) as evidenced by Merchant (supra) in view of Ridgeway (of record).

Claims 47-49, 52, 54, 55, 58-61 and 63 include within their scope, bispecific antibodies that contain engineered C_H3 domains, where the first and second polypeptides interact at an amino acid side chain protuberance of one polypeptide and an amino acid side chain cavity of the other polypeptide. The protuberance and cavity interaction as a means to promote heavy chain heterodimerization is not taught by de Kruif. However, such heterodimerization methods are known in the art as evidenced by the teachings of Ridgeway, which teaches the "knobs-into-holes" strategy, which is a method for altering the C_H3 domain of the heavy chain of a bispecific antibody. Ridgeway teaches that this method has been used to successfully enhance the production of bispecific diabodies (page 620, last paragraph). Therefore, it would have been

prima facie obvious to one of ordinary skill in the art at the time the invention was made have altered the constructs of de Kruif by using the "knobs-into-holes" method for the purpose of dimerizing the bispecific scFv constructs of de Kruif.

13. Claims 47- 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over de Kruif (de Kruif et al., The Journal of Biological Chemistry, 271(13): 7630-7634, 1996, March) as evidenced by Merchant (supra) in view of Ridgeway (of record) and further in view of Hu (Hu, S. et al., Cancer Res. 56: 3055-3061, 1996).

The combination of de Kruif and Ridgeway teach as set forth above. The combination fails to teach bispecific antibody constructs where the non-naturally occurring disulfide bond is between the C_H3 multimerization domains of the first and second polypeptide. However, Hu teaches that single chain Fv constructs can be made divalent by fusing the single chain antibody chains with C_H3 regions (see page 3056, Figure 1); and also teaches the "flex minibody" in which the C_H3 is fused to a hinge region, which contains cysteines for the formation of disulfide bonds, which further stabilize the dimmer (see page 3059, 1st column). Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified de Kruif's bispecific antibodies to have a C_H3 multimerization domain with knobs and holes mutations as taught by Ridgeway, and further to have added hinge region to the C_H3 region so that disulfide bonds could form between the heterodimers.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
May 16, 2006

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SUPERVISORY PATENT EXAMINER